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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,997	10/04/2005	Kai Schiemann	MERCK-3071	6470

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EXAMINER	
MURRAY, JEFFREY H	
ART UNIT	**PAPER NUMBER**
1624	
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07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,997	SCHIEMANN ET AL.	
	Examiner	Art Unit	
	Jeffrey H. Murray	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/04/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/04/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. This action is in response to an application filed on October 4, 2005. There are eighteen claims pending and eighteen under consideration. Claims 1-9, 12 are compound claims. Claims 10, 11 and 15 are process for preparing claims. Claims 13, 14 and 18 are composition claims. Claims 16-17 are use claims. This is the first action on the merits. The application relates generally to chromenoneindole derivatives of the Formula I and finding novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

Priority

2. This application is a non-provisional application 10/551,997, filed October 4, 2005, which is a national stage application of PCT/EP04/02351, filed March 8, 2004, which claims priority from application DE 103 15 285.7, filed April 4, 2003.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without

underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825.
A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

4. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The attempt to incorporate subject matter into this application by reference to Fozard and Kilbinger, Br. J. Pharmacol. 86 (1985), 601P;

Seyfried et. al., Eur. J. Pharmacol., 160, (1989) 31-41; DeVry, Psychpharmacol. 121 (1995), 1-26; Wong et. al., Neuropsychopharmacol., 8, (1993), 23-33; and Fuller et. al., J. Pharmacol. Exp. Ther. 212 (1980), 115-119 is improper because these 5-HTIA receptor binding assays are essential to any one attempting to practice Applicants' clinical claims. Without the data from these assays potential inoperative embodiments cannot be identified and there is no way to determine dosages without this quantitative biological data.

5. The disclosure is objected to because of the following informalities: Page 23 of the specification has Example 2 (Structure 9) incorrectly named. The "-O-ethyl" group attached to the amide should be labeled a "carbamate" group, not an "amide" group. Examiner recommends renaming the Example 2 reference to "ethyl 6-(4-(4-(5-cyano-1H-indol-3-yl)butyl)piperazin-1-yl)-2-oxo-2H-chromen-3-ylcarbamate." to allow the described name to match the structure drawn. Appropriate correction is required.

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Rejections - 35 USC § 101 and 112, 1st

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claim 16-17 provides for the use of the compounds of formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass.

Claims 16-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunla*, 153 USPQ678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim 16 and 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, 1st

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

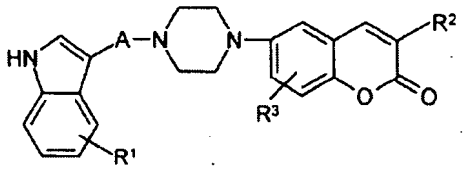
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make chromenoneindoles. Within the application, Claim 1 states a general formula (I):



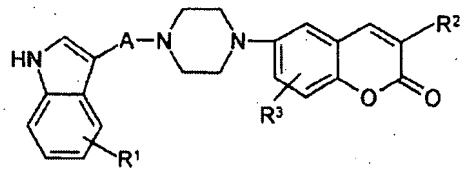
There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist..the examples of the '881 patent do not produce the postulated compounds..there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds

actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

2) *Unpredictability in the art.* It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

The state of the art that is not predictable is whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

3) *Scope of the claims.* The scope of the claims involve all of the thousands of compounds of general formula I:



Thus, the scope of claims is very broad.

4) *Nature of the invention.* The nature of this invention relates generally to chromenoneindole derivatives of Formula I and novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

5) *Level of skill in the art.* The artisan using Applicants invention would be a physician with a M.D. degree, and having several years of experience.

6) *Number of working examples.* The applicant has shown only three working examples in the specification out of the thousands of compounds that fall under the broad Claim 1.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. The examiner suggests deleting "solvates" from Claims 1 and 9.

11. Claims 16-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied

to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above.

Applicants do not state and it is not recognized in the CNS therapeutic arts these assays are correlated to clinical efficacy for the treatment of any human diseases. Applicants explain how to measure the binding to 5-HT_{1A} receptor but do not explain how to determine if the compounds activate (agonize) the two receptors after binding or deactivate (antagonize) the two receptors after binding. According to the specification such measurements are essential to practicing the therapeutic claims. There are no assays describing the 5-$HT_{1D/2A/2C}$ receptors in the specification.

The state of the clinical arts in 5-HT_{1A} receptor related diseases is provided by Gaster (Ann Reports Med. Chem.) who states in the first complete paragraph on page 22 that no clinical utility of 5-HT_{1A} receptor antagonists is known. In the second complete paragraph on page 21, Gaster (Ann Reports Med. Chem.) states that Buspirone, which has utility as an anxiolytic agent, is an agonist at both pre-and post-synaptic 5-HT_{1A} receptor. The state of the clinical arts in D2 antagonist-related diseases is provided by Mortimer (Expert Opinion on Investigational Drugs). Mortimer (Expert Opinion on Investigational Drugs) states in the second complete paragraph, column 2, page 321 that all antipsychotic drugs are D2 antagonists.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown scope of diseases embraced by the term "illnesses which are associated with the serotonin and dopamine neurotransmitter system and in which high-affinity serotonin receptors (5-5-HT_{1A} receptors) and/or dopamine DE receptors are involved." Thus, the scope of claims is very broad. MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based

on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 112, 2nd

12. Claim 1 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 9 are only permitted to claim one invention. The language of Claim 1 and 9 is written in such a way as to claim multiple inventions in one claim, which is not permitted. The claims are indefinite and need to be rewritten. Examiner suggests changing the word "and" at the end of Claim 1 located between "atoms," and "pharmaceutically" to "or." Examiner suggests changing the word "and" at the end of Claim 9 located between "carbonitrile," and "pharmaceutically" to "or." Appropriate correction is necessary.

13. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification does not set forth any steps involved in determining how to identify "diseases in which 5-HT plays a role." Claim 17 lists a number of diseases that Applicants intended to treat but does not clarify if these listed diseases are 5-HT related. It is unclear what

diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. In addition how much involvement or association is required before a diseases falls within these limitations? Hence, the claims are indefinite.

Conclusion

14. Claims 1-18 are rejected.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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